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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/762,594	06/22/2001	Vassilios Papadopoulos		6687

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EXAMINER
BUNNER, BRIDGET E

ART UNIT	PAPER NUMBER
1647	16

DATE MAILED: 04/10/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Offic Action Summary	Applicati n No.	Applicant(s)	
	09/762,594	PAPADOPOULOS ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on th cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) *6-8, 18-33, and 36-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5, 9-17, 34, 35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-40* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 22 June 2001 (Paper No. 3) has been entered in full.

Election/Restrictions

Applicant's election without traverse of Group I, claims 1-17 and 34-35, drawn to an isolated PBR-associated DNA fragment in Paper No. 13 (21 November 2002) is acknowledged.

Claims 18-33 and 36-40 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected group, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 13 (21 November 2002)

Applicant's election with traverse of the nucleic acid sequence of SEQ ID NO: 2 in Paper No. 15 (21 January 2003) is acknowledged. The traversal is on the ground(s) that all of the sequences contained in SEQ ID NOs: 1-5 are related as they all correspond to mouse PBR associated proteins. This is not found persuasive because each of the nucleic acid sequences of SEQ ID NOs: 1-5 broadly encompass 5 different genes or fragments. The nucleic acid sequences of Groups 1-5 are different lengths, composed of different nucleic acids, and are structurally and functionally unrelated, each to each other. The nucleic acid sequence imparts structural and functional differences in each gene which affect properties such as expression levels, tissue specific expression patterns, mRNA half lives, cellular localization of the gene product, etc. Furthermore, each gene encodes a different protein product which is not sufficiently linked by structural or functional features.

The requirement is still deemed proper and is therefore made FINAL.

Claims 6-8 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected group, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 15 (21 January 2003). Applicant elected the nucleic acid sequence of SEQ ID NO: 2, which encodes PAP7. Since claims 6-8 did not read on PAP7, they were withdrawn from consideration.

Claims 1-5, 9-17, and 34-35 are under consideration in the instant application.

Oath/Declaration

1. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

Specification

2. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

3. The disclosure is objected to because of the following informalities:

3a. The Brief Description of Drawings does not specifically refer to Figures 5A-H.

3b. The attempt to incorporate subject matter into this application by reference to a Genbank Accession No. (for example, see page 6 and the claims) is improper because the nucleic acid sequences and amino acid sequences in this database are subject to change over time.

3c. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: "DNA ENCODING PERIPHERAL-TYPE BENZODIAZEPINE RECEPTOR ASSOCIATED PROTEIN 7".

Appropriate correction is required.

Claim Objections

4. Claims 3, 10, and 34-35 are objected to because of the following informalities: Claims 3, 10, and 34-35 recite non-elected SEQ ID NOs/PAPs. Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-5, 9-17, and 34-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated peripheral-type benzodiazepine receptor (PBR)-associated protein 7 (PAP7) DNA sequence of SEQ ID NO: 2 or for an isolated DNA sequence that encodes the PAP7 amino acid sequence of SEQ ID NO: 7, does not reasonably provide enablement for an isolated PBR-associated protein (PAP) DNA fragment or any portion thereof. The specification is not enabling for an isolated and purified DNA fragment which encodes a PBR-associated protein. The specification is also not enabling for any DNA fragments of SEQ ID NO: 2 comprising at least 30 nucleotides or an isolated DNA fragment which encodes a peptide of PBR-associated protein, said DNA comprising a sequence specified in Genbank Accession Nos. AF022770 or AF020338 or a fragment of said sequence comprising at least 30 nucleotides. The specification is not enabling for an isolated PAP7 DNA fragment or natural or synthetic variant or a peptide fragment comprising at least 10 amino acids. The

specification is not enabling for primers or oligonucleotides specific for PAP RNA or cDNA or for methods of increasing a PAP in a cell. Finally, the specification is not enabled for a method for increasing PAP7 in a cell by introducing into said cell a PAP nucleic acid such that the nucleic acid is expressed and PAP7 is produced in the cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims also recite a recombinant DNA construct comprising a vector and PAP DNA fragment. The claims recite a host cell transformed with a recombinant DNA construct and a method for producing PAP peptide.

The specification teaches that PAP7 binds to PBR (peripheral-type benzodiazepine receptor) (pg 40, 44-45), which mediates cholesterol delivery and steroid formation. The specification also discloses that when DNA encoding a partial PAP7 sequence (192 amino acids of C-terminal sequence) is transfected into MA-10 cells, the PAP7 transfectants have significantly reduced levels of progesterone production as compared to control (pg 47, lines 12-26). The specification indicates that this result could indicate that the transfected PAP7 fragment is not fully functional and reduces the interaction between PBR and endogenous PAP7 (pg 51, lines 18-26). The specification discloses that variants of the nucleic acid molecules of the present invention may occur naturally or non-naturally by mutagenesis techniques (pg 17, lines 30-35 to pg 18, lines 1-4). Variants include those produced by nucleotide substitution, deletion, addition and alteration in the coding regions may produce conservative or nonconservative amino acid substitutions, deletions, or additions (pg 18, lines 5-9). However, the specification does not disclose methods or examples to enable one skilled in the art to obtain a "natural

variant" of DNA (SEQ ID NO: 2) encoding PAP7 or any allelic variants of SEQ ID NO: 2, particularly from other species besides human. The specification does not disclose the chromosomal locus for PAP7. Since allelic variants must be at the same locus as the PAP7 gene, it would be undue experimentation for one skilled in the art to identify the locus and map variants to determine which are alleles. Furthermore, the specification does not disclose any primers/oligonucleotides specific for the RNA or cDNA of any PAP. Undue experimentation would be required by the skilled artisan to determine the appropriate primer/oligonucleotide sequence suitable for hybridization or amplification of all possible PAPs. Additionally, the specification does not teach functional DNA fragments of any PAP, including PAP7. For example, as discussed above, the partial PAP7 sequence transfected into MA-10 cells has little or no functional activity as compared to wild-type PAP7. The specification also does not teach functional or structural characteristics of any other DNA sequences other than SEQ ID NO: 2 (which encodes PAP7) in the context of a cell or organism.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no

substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein and DNA which are tolerant to change (e.g. such as by amino acid or nucleic acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427).

Furthermore, the Examiner has interpreted claim 35 as reading upon gene therapy since the claim recites introducing a PAP nucleic acid into *a cell*. There is no limitation in the claim reciting what type of cell is utilized in the method. The specification does not teach any methods or working examples that indicate a PAP nucleic acid is introduced and expressed in the cell of

an organism. The specification discloses that "agents which decrease the level of PAP (i.e. in a human or an animal) or reduce or inhibit PAP activity may used in the therapy of any disease associated with the elevated levels of PAP. Similarly agents which increase the level of PAP or activate PAP activity may be used in the therapy of any disease associated with reduced levels of PAP" (pg 31, lines 28-34). The specification teaches that agents can be administered as DNA (pg 32, lines 4-15). However, this is not adequate guidance, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. For example, the specification does not teach what type of vector would introduce the PAP nucleic acid into the cell or in what quantity and duration. Relevant literature teaches that since 1990, about 3500 patients have been treated via gene therapy and although some evidence of gene transfer has been seen, it has generally been inadequate for a meaningful clinical response (Phillips, A., J Pharm Pharmacology 53: 1169-1174, 2001; abstract). Additionally, the major challenge to gene therapy is to deliver DNA to the target tissues and to transport it to the cell nucleus to enable the required protein to be expressed (Phillips, A.; pg 1170, ¶ 1). Phillips also states that the problem with gene therapy is two-fold: 1) a system must designed to deliver DNA to a specific target and to prevent degradation within the body, and 2) an expression system must be built into the DNA construct to allow the target cell to express the protein at therapeutic levels for the desired length of time (pg 1170, ¶ 1). Therefore, undue experimentation would be required of the skilled artisan to introduce and express a PAP nucleic acid into the cell of an organism. Additionally, the method of claim 35 is unpredictable and complex wherein one skilled in the art may not necessarily be able to introduce and express a PAP nucleic acid in the cell of an organism or be able to produce a PAP protein in that cell.

Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity and to introduce and express a PAP nucleic acid into a cell of an organism, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity and how to introduce a PAP nucleic acid in the cell of an organism to be able produce that PAP, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function and the unpredictability of transferring genes into an organism's cells, and the breadth of the claims which fail to recite any structural or functional limitations or any cell type limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

7. Claims 1-5, 9-17, and 34-35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Specifically, the claims are directed to an isolated PBR-associated protein (PAP) DNA fragment or any portion thereof. The claims recite an isolated and purified DNA fragment which encodes a PBR-associated protein and DNA fragments of SEQ ID NO: 2 comprising at least 30 nucleotides. The claims recite an isolated PAP7 DNA fragment or natural or synthetic variant or a peptide fragment comprising at least 10 amino acids. The claims are directed to an isolated DNA fragment which encodes a peptide of PBR-associated protein, said DNA comprising a

sequence specified in Genbank Accession Nos. AF022770 or AF020338 or a fragment of said sequence comprising at least 30 nucleotides. The claims also recite primers or oligonucleotides specific for PAP RNA or cDNA or for methods of increasing a PAP in a cell. The claims recite a recombinant DNA construct comprising a vector and PAP DNA fragment. The claims recite a host cell transformed with a recombinant DNA construct and a method for producing PAP peptide.

The specification teaches a PAP7 polynucleotide and polypeptide (SEQ ID NO: 2 and SEQ ID NO: 7, respectively). The specification also discloses that variants of the nucleic acid molecules of the present invention may occur naturally or non-naturally by mutagenesis techniques (pg 17, lines 30-35 to pg 18, lines 1-4). Variants include those produced by nucleotide substitution, deletion, addition and alteration in the coding regions may produce conservative or nonconservative amino acid substitutions, deletions, or additions (pg 18, lines 5-9). However, the specification does not teach functional or structural characteristics of the polynucleotides in the context of a cell or organism. The description of one PAP7 polynucleotide species (SEQ ID NO: 2) and one PAP7 polypeptide species (SEQ ID NO: 7) is not adequate written description of an entire genus of functionally equivalent polynucleotides and polypeptides which incorporate all variants and fragments of the PAP7 polynucleotide comprising SEQ ID NO: 2 and the PAP7 polypeptide comprising SEQ ID NO:7. Furthermore, the description of one PAP7 polynucleotide species (SEQ ID NO: 2) and one PAP7 polypeptide species (SEQ ID NO: 7) in the instant specification is not adequate written description for an entire genus of functionally equivalent polynucleotides and polypeptides of the sequences

specified in Genbank Accession Nos. AF022770 or AF020338 of fragments, especially since the sequences disclosed in this database may be subject to change with time.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed"* (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

With the exception of the sequences referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only an isolated peripheral-type benzodiazepine receptor (PBR)-associated protein 7 (PAP7) DNA sequence of SEQ ID NO: 2 or an isolated DNA sequence that encodes the PAP7 amino acid sequence of SEQ ID NO: 7, but not the full breadth of the claims meet the

written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

35 USC § 112, second paragraph

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-5, 9-17, and 34-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. Regarding claims 1-5, 9-17, and 34-35, the acronyms "PBR" and "PAP" render the claims vague and indefinite. Abbreviations should be spelled out in all independent claims for clarity.

11. Claim 34 is indefinite because the elements recited in the claim do not constitute proper Markush groups. The claim is indefinite in the alternative use of "and/or" because it is not clear what controls which of these limitations. See MPEP § 2173.05(h).

12. Claim 35 is indefinite because the claim does not have a step that clearly relates back to the preamble. For example, there is no step indicating that PAP is increased in a cell.

Conclusion

No claims are allowable.

The art made of record and not relied upon is considered pertinent to applicant's disclosure:

General references about the peripheral-type benzodiazepine receptor and its role in steroidogenesis and cholesterol transport:

Rao RM et al. Endocr Res. 28(4):387-394, 2002.

Papadopoulos, V et al. Endocr Res. 24(3-4):479-487, 1998.

Papadopoulos V et al. Steroids. 62(1):21-28, 1997.

Papadopoulos V et al. J Steroid Biochem Mol Biol. 53(1-6):103-110, 1995.

Li, H et al. Endocrinology. 139(12):4991-4997, 1998.

Hauet et al. Endocr Res. 28(4):395-401, 2002.

Culty M et al. J Steroid Biochem Mol Biol. 69(1-6):123-130, 1999.

Zisterer et al. Biochem Soc Trans. 23(2):371S, 1995.

Reference that teaches part of the PAP7 DNA sequence:

Li et al. Accession No. AF022770, 02 Oct 1997.

Reference that teaches PAP7 and its localization and function:

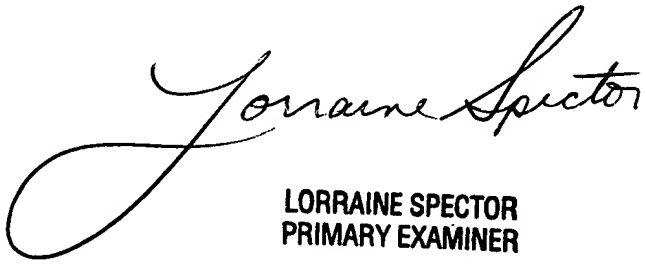
Li, H et al. Molec Endocrinol 15(12) : 2211-2228, 2001.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (703) 305-7148. The examiner can normally be reached on 8:30-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 872-9305.

BEB
Art Unit 1647
April 4, 2003



LORRAINE SPECTOR
PRIMARY EXAMINER